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Contract Title: Short-wavelength countermeasures for circadian desynchrony
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EXECUTIVE SUMMARY

Exposure to light at critical phases of the circadian cycle entrains circadian rhythms. Exposure of humans to bright light for an hour or more at the right phase of the circadian cycle produces significant phase shifts of circadian rhythms speeding recovery from jet-lag, and optimizing cognitive functionality and restorative sleep. Our work on mice produced the unexpected result that exposure to intermittent millisecond flashes of light distributed over an hour for a total of only 120 msec. of light can produce maximum phase shifts. Our specific aims were: 1) build a prototype, programmable photodiode based device to deliver light flashes of 1 to 3 msec duration to a person's eyes, 2) conceptualize a commercializable wearable device containing an algorithm that will provide an automatic flash delivery schedule, 3) test whether or not the human circadian system is susceptible to phase resetting by appropriately delivered millisecond flashes of light, and 4) plan experiments to define optimal stimulation protocols. We built the prototype, we have also built prototypes of wearable commercializable devices with a flash delivery algorithm. Tests of flash effects on human circadian rhythms are underway. And, our plans for future experiments have been incorporated into our Phase II proposal.

RESULTS OF PHASE I WORK

Specific Aims:

1. AVAcore Technologies, Ann Arbor Mich., will build a prototype, programmable photodiode based device that will be able to deliver light flashes of 1 to 3 msec duration to a person's eyes at a distance of up to 5 meters at an intensity between 1 and 100 μJ/cm² at a frequency ranging from 6 flashes per minute to 6 flashes per hour. The programmability of the device will enable us to adjust the intensity and frequency of the flashes.
2. Based on results of studies we will do with this device, AVAcore will conceptualize a commercializable embodiment of the technology in anticipation of phase II. This device will contain an algorithm that will automatically adjust the intensity of the flashes for ambient light levels and will also provide an automatic delivery schedule based on a comparison of home time and destination time.
3. Stanford will use the AVAcore prototype devices to test whether or not the human circadian system is susceptible to phase resetting by appropriately delivered millisecond flashes of light. These experiments will be done on volunteers in an temporal isolation room using a constant routine bed rest protocol. The dependent variable will be the circadian rhythm in melatonin as detected in saliva samples.
4. In anticipation of Phase II, Stanford will use the results obtained to plan additional series of experiments that will explore the optimal stimulation protocol and the sensitivity of the human circadian system to this mode of phase shifting across all phases of the circadian day.

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14. ABSTRACT
Exposure to light at critical phases of the circadian cycle entrains circadian rhythms. Exposure of humans to bright light for an hour or more at the right phase of the circadian cycle produces significant phase shifts of circadian rhythms speeding recovery from jet-lag, and optimizing cognitive functionality and restorative sleep. Our work on mice produced the unexpected result that exposure to intermittent millisecond flashes of light distributed over an hour for a total of only 120 msec. of light can produce maximum phase shifts. Our specific aims were: 1) build a prototype, programmable photodiode based device to deliver light flashes of 1 to 3 msec duration to a person's eyes, 2) conceptualize a commercializable wearable device containing an algorithm that will provide an automatic flash delivery schedule, 3) test whether or not the human circadian system is susceptible to phase resetting by appropriately delivered millisecond flashes of light, and 4) plan experiments to define optimal stimulation protocols. We built the prototype, we have also built prototypes of wearable commercializable devices with a flash delivery algorithm. Tests of flash effects on human circadian rhythms are underway. And, our plans for future experiments have been incorporated into our Phase II proposal.

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Progress Report:

We completed SA 1. We obtained a photograph strobe unit and built a programmable controller for it that enables programming of single flash duration, frequency, and intensity, as well as time of day for beginning and ending of flash sequence (Figure 1).

Figure 1. Commercial 500 watt strobe flash unit with custom made control unit. The control unit enables setting of flash frequency, flash intensity, and delivery time.

We made much more progress on SA 2 than proposed due to a fortuitous partnering with NeuroTech who was interested in developing applications for LEDs with different wave length emissions. They were willing to take a license for the technology from Stanford to be able to work with AVAcore and the Stanford Research Team to develop and test a commercializable circadian phase shifting product. NeuroTech has not required any financial support from us to facilitate their role in the development process. Working with them, we have been able to develop prototypes of goggles and sleep masks that incorporate different arrays of LEDs for light flash delivery. We developed a controller that times the flash delivery in terms of time of day, flash frequency, flash pattern, and duration of flash sequence. We also developed an algorithm based on the human circadian phase response curve that enables the device to automatically determine time of flash delivery based on three factors: home time, normal bed time, and local time (Figure 2).

Figure 2. Prototype system for delivery of LED generated light flashes to the eyes through either a sleep mask (left side) or goggles (right side). The control unit is incorporated into an MP3 player shown in the center.

Our progress on SA 3 is incomplete due to delays in getting the new time isolation unit completed and operational at the Palo Alto VA Hospital. We obtained our IRB approval for these experiments, but did not have a sufficiently secure time isolation unit to run the experiments. That facility is up and running (Figure 3), and we are running our 5 subjects now according to the following schedule.

Subject	First visit	Second visit
1	complete	7/1/08
2	7/15/08	7/29/08
3	7/22/08	8/5/08
4	8/12/08	8/26/08
5	8/19/08	9/2/08

We were hoping to get these data collected sooner, but have run into repeated problems. First, if a survey shows that the subject has not maintained a regular sleep routine for the prior 2 weeks, we have to reschedule the visit. Second, we are limited by the availability of all night nursing staff, and third, we have to accommodate the subjects schedules. We are trying to speed up the schedule, but it will still extend into September. We will have melatonin results from the first subject by Mid July. We will file the completed results as a supplementary report.

SA 4 completion is essentially the work plan for this Phase II proposal. Based on our analyses of the circadian phase response curve and previous experience with light sensitivity studies in humans carried out by Dr. Zeitzer, we have modified and refined our plans for human studies in the time isolation unit so that we can get maximum data for the amount of time we have to keep subjects in the unit. By making the experimental design efficient, we will be able to test more variables associated with the light delivery than simple exposure to strobe flashes.

Conclusion:

The overall goal of our proposed research and development plan is to build the capacity to test the hypothesis that brief flashes of bright light delivered at intervals of 1 to 5 minutes for an hour will be sufficient to achieve maximum phase shifts of human circadian rhythms. In Phase I we have built to prototype device for experimental purposes. We have also built a wearable prototype with a built-in algorithm that delivers light flashes at the appropriate circadian time to achieve the phase shifts necessary to mitigate jet lag. We have set up a time isolation unit to evaluate phase shifts in humans by following their melatonin secretion peaks. Trials are underway, and we have planned an experimental program to fully characterize and optimize the flash phase shifting technology in humans.

Figure 3. Inside the time isolation unit with the strobe unit in place. The intensity of the flash experienced by the subject is 130 lux. The background illumination intensity of the room is total darkness during the sleep period <1 lux during all waking hours,